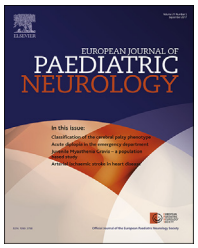
Official Journal of the European Paediatric Neurology Society



Original article

Neonatal hypoglycemia: A wide range of electroclinical manifestations and seizure outcomes

Ebru Arhan, Zeynep Öztürk, Ayşe Serdaroğlu, Kürşad Aydın, Tuğba Hirfanoğlu, Yılmaz Akbaş*

Gazi University, Faculty of Medicine, Department of Pediatric Neurology, Turkey

ARTICLE INFO

Article history:
Received 9 July 2016
Received in revised form
21 March 2017
Accepted 24 May 2017

Keywords:
Neonatal hypoglycemia
Electroclinical
Outcome
Intractable epilepsy
Glucose

ABSTRACT

Purpose: We examined the various types of epilepsy in children with neonatal hypoglycemia in order to define electroclinical and prognostic features of these patients.
Method: We retrospectively reviewed the medical records of patients with a history of symptomatic neonatal hypoglycaemia who have been followed at Gazi University Hospital Pediatric Neurology Department between 2006 and 2015. Patients with perinatal asphyxia were excluded. Details of each patient's perinatal history, neurological outcome, epilepsy details, seizure outcome and EEG and brain MRI findings were reviewed.
Results: Fourty five patients (range 6 mo–15 y) with a history of symptomatic neonatal hypoglycaemia were included the study. Epilepsy developed in 36 patients and 23 of them had intractable epilepsy. All patients had occipital brain injury.
Conclusion: We observed that most of the patients, either manifesting focal or generalized seizures, further develop intractable epilepsy. This finding establishes neonatal hypoglycemia as a possible cause to be considered in any case of intractable epilepsy.

1. Introduction

Glucose is the primary energy source of the human brain, therefore highly susceptible to hypoglycemic damage with a high risk of neurologic handicap including; cerebral palsy, intellectual disability, blindness and epilepsy.[1–4] Hypoglycemic brain injury is a recognized insult that triggers seizures and is typically associated with both focal and generalized epilepsy. The frequency of epilepsy after symptomatic neonatal hypoglycaemia is greater than 50%.[5–7] However, the spectrum of hypoglycemic brain injury resulting in epilepsy is unclear. Most of existing literature on this topic is focused on the incidence of seizures in large cohorts of epileptic patients after neonatal hypoglycemia with only a few studies describing the clinical, EEG, and syndromic aspects specifically.[5,7,8] To add to the knowledge base of this subject, in the

* *Corresponding author*. Gazi University, Faculty of Medicine, Department of Pediatric Neurology, Besevler, Ankara 06510, Turkey. Fax: +90 312 21501 43.
E-mail address: zeynep1220@yahoo.com (Z. Öztürk).
http://dx.doi.org/10.1016/j.ejpn.2017.05.009
1090-3798/

present study, we examined the various types of epilepsy in children with neonatal hyperglycemia in order to define electroclinical and prognostic features of these patients. This information will enable earlier identification of patients, thereby preventing the progression. To our knowledge, this study is the largest report on a detailed analysis of the spectrum of epilepsy in neonatal hypoglycemia.

2. Material method

A retrospective electronic chart review using the key words "neonatal hypoglycemia", "epilepsy" was performed to identify patients who had a neurological handicap after neonatal hypoglycemia and subsequently followed at Gazi University Hospital Pediatric Neurology Department between 2006 and 2015. Gazi University Hospital Pediatric Neurology Department provides primary to tertiary levels of care for children with neurological disorders. The routine and video-EEG laboratories perform about 1500 pediatric EEGs per year. A total of 892 patients' charts were reviewed and, of these, 45 patients were found who were followed with neurological disorders after neonatal hypoglycemia. Of these, 36 patients were followed with epilepsy after neonatal hypoglycemia. These 36 subjects form the basis of the current report. Patients with a history of perinatal asphyxia and patients without documented hypoglycemia and apgar score at 5 min after delivery less than 7 were excluded from the study. Hypoglycemia, was defined as a whole blood glucose concentration of less than 47 mg per deciliter (2.6 mmol per liter). The study was approved by the hospital's ethics committee. A total of 36 subjects (26 male, 10 female, 11 mo–18 y 5 mo; mean age 10 y 5 mo, at the time of review) who developed epilepsy after neonatal hypoglycemia were identified. Multiple clinical variables in these 36 subjects were reviewed: neonatal hypoglycemia details, perinatal history, epilepsy details, imaging characteristics and neurological outcome. Neonatal hypoglycemia was classified by using a classification based on the clinical setting, the presence of symptoms, the duration and severity of hypoglycemia.[9,10] According to this classification, patients were divided into two groups[1]; Early transitional neonatal hypoglycemia: typically occurring in the first 6–12 h after sudden withdrawal of maternally derived substrate at birth and resolved within 5 days or[2] severe persistent neonatal hypoglycaemia, caused by specific primary enzymatic or metabolic-endocrine abnormalities involving glucose homeostasis. Neonatal hypoglycemia details included; risk factors (maternal conditions like gestational diabetes, preeclampsia, eclampsia), neonatal conditions (gestational age, gestational weight, sepsis, hyperbilirubinemia, intrauterine growth retardation), duration of hypoglycemia. Etiological investigation of neonatal hypoglycemia was performed by laboratory tests including; amino acid profile, thyroid hormones (T4/TSH), growth hormone, insulin, cortisol and acylcarnitines, and urine organic acids, ketone bodies. Hypoglycemia symptoms including seizures, poor feeding, hypothermia, apnea, altered consciousness, hypotonia were noted. Seizure onset, semiologic features, frequency, distribution, duration of the seizures, drug treatment, seizure outcome were analyzed from the medical records. Onset of epilepsy was accepted as the first seizure after the neonatal period. The epileptic syndromes were analyzed in detail. EEG of each patient was reviewed with respect to background abnormality (slowing of the background EEG rhythm, intermittent or continuous generalized, localized or regional slowing), the localization (generalized, focal, multifocal), morphology spike, polyspike, sharp wave, spike wave, sharp slow wave, and polyspike wave, and topography of interictal epileptiform discharges (IEDs). The classification of seizures was based on the clinical and EEG findings according to the criteria of International League Against Epilepsy.[11] In all cases, cranial MRI was performed with epilepsy protocol using superconducting magnets with multichannel head coils in the supine position with a 1.5 T MRI (GE SIGNA EXCITE, Milwaukee, USA). Epilepsy protocol included axial and sagittal T1 weighted, axial T2 weighted, oblique coronal FLAIR perpendicular to the long axis of both hippocampi, and 3D inversion recovery (IR). The whole brain volumetric series were acquired using a 3D IR technique with a slice of 1 mm thickness, zero interslice gap, 256 × 222 matrix size, and a single signal average. T2 weighted oblique axial images through the long axis of both hippocampi consisting of 20 slices were also obtained with 3 mm slice thickness and 0.75 mm interslice gap. All MRI slices were re-evaluated by K.A., who is most experienced and educated physician in MRI interpretation in the group.

Statistic analysis was performed with the SPSS statistical analysis program using the x^2 test. P values of less than 0.05 were regarded statistically significant.

3. Results

3.1. *Clinical manifestations*

Twenty-nine patients were delivered at term, and seven patients were delivered prematurely. One infant was the product of twin pregnancy. All patients had Apgar scores >8 at 5 min. One patient had a history of exposure to valproate during the first three months of pregnancy. At presentation, all patients had signs and symptoms of acute neurological dysfunction associated with neonatal hypoglycaemia, with neonatal convulsions evident in 20 (18 of them in the first 72 h of life), apnea in 3 and irritability in 3. Ten patients had prenatal and perinatal problems (maternal diabetes (n:2), preeclampsia (n:4), prematurity (n:7)) that made them prone to hypoglycemia and/or medical problems other than hypoglycemia. Three patients were small for gestational age with birth weights of 2000–2250 g, delivered at term. Three patients had indirect hyperbilirubinemia requiring phototherapy; one patient had partial exchange transfusion for polycythemia. Neonatal sepsis was diagnosed in three patients with a positive blood culture in all. All infants had routine blood investigations performed for neonatal hypoglycaemia. Transient neonatal hypoglycaemia was diagnosed in 33 children, all of them had feeding difficulty. Persistent neonatal hypoglycemia was diagnosed in three children, two of them had hyperinsulinism and the other patient in the persistent group had panhypopituitarism. The minimum blood glucose ranged between 5 and 38 mg/dl (mean ± SD, 21.63 ± 1.33 mg/dl). Duration of neonatal hypoglycemia ranged from 6 h to 3 days